AMENDMENTS TO THE DRAWINGS

Attached please find 5 sheets of Replacement Drawings.

Attachment: Five (5) Replacement Sheets

REMARKS

Claims 1-12 are all the claims pending in the application. Claims 1-11 have been amended to more clearly point out the claimed feature of the invention. Claim 12 has been withdrawn from consideration. Support for amendments to the claims may be found by throughout the specification and claims, for example, on page 2, lines 14-21. No new matter has been introduced. Entry of the amendments and reconsideration of the application are respectfully requested.

Drawings

Fig. 1 is objected to. Applicants submit five (5) sheets of Annotated Drawings and five (5) sheets of Replacement Drawings, each including Fig. 1.

Claim Rejections under 35 U.S.C. § 112

Claims 1-11 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-11 have been amended to more clearly define the presently claimed invention. For example, currently presented claim 1 recites "A polyethylene glycol (PEG)-polypeptide homodimer complex, comprising a first PEG molecule; and two molecules of a polypeptide, wherein the two molecules of the polypeptide are linked to each other via the first PEG molecule to form a polypeptide-first PEG-polypeptide complex, and the polypeptides of the polypeptide-first PEG-polypeptide complex each are bonded to a second PEG molecule having a larger molecular weight than that of the first PEG molecule to form a second PEG-polypeptide-first PEG-polypeptide-second PEG complex and wherein the first PEG is covalently bonded to the

polypeptides at an N-terminal residue or a C-terminal residue of the polypeptides." Therefore, the currently presented claim 1 and its dependent claims states more clearly the features of the first PEG and the second PEG molecules and the claimed polyethylene glycol (PEG)-polypeptide homodimer complex.

Therefore, Applicants respectfully submit that the amendments render the rejection moot and it is respectfully requested that the rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 102

Claims 1, 3, 4, 6, 7, 10 and 11 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Braxton (US 5,766,897) ("Braxton"). The applicants respectfully traverse the rejection for the following reasons.

i) Feature of the Present Invention

The currently presented claim 1 is directed to a polyethylene glycol (PEG)-polypeptide homodimer complex, comprising a first PEG linkermolecule; and two molecules of a polypeptide, wherein the two molecules of the polypeptide are connected linked to each other via the first PEG linker molecule to form a polypeptide-first PEG-polypeptide complex, and each of the two molecules of the polypeptides of the polypeptide-first PEG-polypeptide complex each is bonded to modified with one molecule of a second PEG molecule having a larger molecular weight than that of the first PEG molecule (i.e., M.W of the first PEG molecule < M.W of the second PEG molecule) to form a [second PEG] – [polypeptide] – [first PEG] – [polypeptide] – [second PEG] complex,. and wherein the first PEG is covalently bonded to the polypeptides at the N-terminal or C-terminal residues of the polypeptides.

ii) Braxton's teaching

By way of review, Braxton teaches a PEG-polypeptide dimeric complex (see col. 13, line 56) having general formula of [polypeptide 1]-S-[PEG]-S-[polypeptide 2], polypeptides 1 and 2 being the same or different, wherein the two polypeptides are connected via the PEG linker with sulfide bond (-S-) and the polypeptides are inherently modified by the same PEG molecule as the PEG linker.

iii) Comparison of the Present Invention with Braxton

Contrary to the Office Action's view, Braxton fails to disclose all and every elements of the currently presented claims, as described below.

As described in pages 1 and 2 of the specification of the present application, in order to improve the stability of a polypeptide which has physiological activity, the chemical modification thereof with a highly soluble macromolecule such as PEG, which prevents the polypeptide from contacting with proteases, has been widely used. However, such PEGylated polypeptide tends to have low activity as the molecular weight of PEG increases, because PEG randomly forms a covalent bond with a free lysine residue of the polypeptides.

In order to overcome the above mentioned problem, the applicants have developed the inventive PEG-polypeptide homodimer complex prepared by making a homodimer by connecting two molecules of a polypeptide to each other via a first PEG molecule to minimize the decrease in the physiological activity thereof; and modifying the respective polypeptide with a second PEG molecule, which has a larger molecular weight than that of the first PEG molecule, to increase the in vivo stability of the polypeptides to prolong in vivo activity thereof (see Test Examples 5 and 6 of the specification).

However, to overcome the above mentioned problem, Braxton teaches a method of selectively PEGylating a specific site of a polypeptide to maintain the activity of the polypeptide, but it is silent about such distinctive features discussed above in terms of enhancing the *in vivo* activity of the polypeptides.

Accordingly, Braxton fails to teach the PEG-polypeptide homodimer complex of the currently presented claim 1. For example, among others, Braxton fails to teach that the two polypeptide molecules are linked to a first PEG as well as to a second PEG, the second PEG having a larger molecular weight than that of the first PEG.

Therefore, it is believed that claim 1 and its dependent claims are not anticipated by Braxton. It is respectfully requested that the rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 2, 5, 8 and 9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Braxton as applied to claims 1, 3, 4, 6, 7, 10 and 11 above, and further in view of Kay *et al.* (US 2002/0077294) ("Kay"). The applicants respectfully traverse the rejection for the reasons provided below.

i) Braxton and Kay

As mentioned above, Braxton teaches a PEG-polypeptide dimeric complex (see col. 13, line 56) having general formula of [polypeptide 1]-S-[PEG]-S-[polypeptide 2], but does not expressly teach specific PEG groups as recited in currently presented claims 2, 5, 8 and 9.

Furthermore, Kay discloses polypeptide derivatives in which a protein is linked to a nonproteinaceous moiety (e.g., a polymer) in order to modify its properties (paragraph 0146).

PEG is as an example of the polymer (paragraph 0148). Kay also teaches PEG modification at the amino terminus of the protein (paragraph 0157), the polymer having a molecular weight of 2-100 kDa (paragraph 0149), protein dimmers via crosslinkers (paragraph 0161), propionaldehyde (i.e., propionic aldehyde) groups on PEG (paragraph 0148), reactive groups such as maleimide, and the polymers which may be branched or unbranched (paragraph 0149).

ii) Comparison of the Claims with Braxton and Kay

a) Comparison of the claims with Braxton

As mentioned above, the present invention described in the currently presented claim 1 is different from Braxton in that the PEG-polypeptide homodimer complex is prepared by making a homodimer by connecting specific parts of two molecules of a polypeptide to a first PEG molecule to minimize the decrease of the biological activity thereof; and modifying the polypeptides of the homodimer with a second PEG molecule having a larger molecular weight than that of the first PEG molecule to increase the *in vivo* stability of the polypeptide to prolong the polypeptide's *in vivo* activity.

Specifically, as shown in Test Example 6, the PEG-polypeptide homodimer complex according to has a prolonged half-life, while maintaining the activity of the polypeptide.

As discussed above, Braxton fails to teach the PEG-polypeptide homodimer complex of the currently presented claim 1. For example, among others, Braxton fails to teach that the two polypeptide molecules are linked to a first PEG as well as to a second PEG, the second PEG having a larger molecular weight than that of the first PEG.

b) Comparison of the claims with Kay

Kay does not cure the defects of Braxton's teaching. The Office Action asserts that Kay discloses specific PEG groups as recited in claims 2, 5, 8 and 9.

Even though Kay teaches a protein linked to a PEG (molecular weight of 2-100 kDa) (paragraph 0149), and a dimer of proteins each lined to the other via a cross linker such as bivalent PEGs (paragraph 0161), it does not teach "a second PEG-polypeptide-first PEG-polypeptide-second PEG complex wherein the first PEG is covalently bonded to the polypeptides at an N-terminal residue or a C-terminal residue of the polypeptides, and the second PEG molecule having a larger molecular weight than that of the first PEG molecule," as recited in the currently presented claim 1.

Therefore, it is respectfully requested that the rejection be withdrawn.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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